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09/918,036	07/30/2001	Kiran Madura	266/165	1466

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PERKINS COIE LLP
POST OFFICE BOX 1208
SEATTLE, WA 98111-1208

EXAMINER	
WALICKA, MALGORZATA A	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 06/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/918,036	MADURA, KIRAN	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 13-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The reply to Restriction Requirement filed on May 3, 2004 is acknowledged. Claims 1-18 are pending in the application. Elected claims 6 to 12 are the subject of this Office Action. Claims 1-5 and 13-18 are withdrawn from examiner's consideration as drawn to a non-elected invention.

Detailed Office Action

1. Restriction/Election

Applicant's election with traverse of Group II drawn to a DNA construct and method for assessing the proliferative potential of malignant cells, classified in class 435, subclass 6, is acknowledged. Applicants traverse the restriction that is rewritten below.

"Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claim 1-5, drawn to a method for rapid and efficient purification of proteasome, classified in class 530, subclass 412.

II. Claim 6-12, drawn to a DNA construct and method for assessing the proliferative potential of malignant cells, classified in class 435, subclass 6.

III. Claim 13-15, drawn to a DNA construct encoding a thermostable fusion protein, classified in class 530, subclass 23.4.

IV. Claim 16 -18, drawn to a DNA construct encoding a fusion protein for selecting for drug resistance in mammalian cells, classified in class 435, subclass 7.23.

Inventions are different from each other for the following reasons.

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are two unrelated methods having different steps and effects. The methods are not disclosed as capable of use together.

Inventions I and III-IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions, the methods of purification of proteasome is unrelated to a DNA construct encoding a thermostable protein or protein used in selecting for drug resistance. The inventions are not disclosed as capable of use together.

Inventions II and III-IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the DNA construct and the method of assessing the proliferative potential of malignant cells are not disclosed as capable of working together with DNA constructs encoding a thermostable fusion protein or protein used in selecting for drug resistance.

Inventions III and IV are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the DNA encoding a thermostable fusion protein and DNA construct encoding a protein used in selecting for drug resistance are different chemical entities.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C. F. R. paragraph 1.48 (b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filled petition under 37 C.F.R. paragraph 1.48 (b) and by the fee required under CFR paragraph 1.17(h)."

Applicants' traverse the restriction on the ground that

"In accordance with MPEP §803, there are two criteria which must be met for a proper restriction requirement. The first is that the inventions

be independent or distinct; the second is that there would be serious burden on the examiner if the restriction is not required. Searching for a DNA construct encoding a thermostable fusion protein in addition to searching for a DNA construct encoding a fusion protein for selecting for drug resistance in mammalian cells does not present a serious burden to the Examiner. A search encompassing the fussion protein themselves would necessarily reveal prior art references describing their use."

The traverse pertains to all IV inventions indicated by the examiner. Applicants enumerate two prerequisites for restriction requirement, i.e., the invention should be independent or distinct and a serious burden on examiner, and argue that searching Groups I-IV together does not appear to be a serious burden.

Applicants are kindly reminded that restriction involves four factors: distinctness, independence, classification and burden to the examiner.

Claims 1-18 filed in the application are directed to two distinctive and independent methods that use fusion proteins of different chemical structures as well as two further fusion proteins whose chemical structures differ from each other and are different from the fusion proteins of Group I and II. Applicants are reminded that 37 CFR 1.475 does not provide for multiple products or methods within a single application.

As to the searches, though the searches of fusion proteins are overlapping searches, the searches of the inventions as restricted are not coextensive,

because of distinctness, independence and different classification. The search of Group I would require search of class 530, subclass 412, which is not necessary for any other Group. Search of class 435, subclass 6, is necessary only for Group II, but not for any other group, etc. In addition, different searches of literature are required for Groups I to IV.

In conclusion, although Applicants arguments are fully considered they are found not persuasive and the restriction is made FINAL. Claims 6-12 are the subject of this Office Action. Claims 1-5 and 13-18 are withdrawn from consideration as they are directed to the nonelected inventions; see 37 CFR 1.141(b).

2. Objections

The specification is objected to because the cross-reference to the previous application and patent is not updated.

3. Rejections

3.1. 35 USC, section 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 6-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The base claim 6 is unclear in reciting "the half-life of said fusion gene". It is assumed for examination purposes that Applicants mean "the half-life of the polypeptide encoded by said fusion gene".

The base claim 6 recites "a target cells" in the third line. There is insufficient antecedent basis for this limitation in the claim because the method is intended to be used with malignant cells.

The base claim 6 is rejected because it recites the limitations "rapidly growing cell" and "quiescent cell" in part b). There is insufficient antecedent basis for this limitation in the claim, because part a) of the claim is directed to assessing the proliferative potential of malignant cells and not to cells as such.

The terms "short", "rapidly" and "longer" in claim 6 are relative terms, which render the claim indefinite. The terms "short", "rapidly" and "longer" are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

2.2. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear,

concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.2.1. Lack of written description

Claim 6 –12 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a large and variable genus of fusion proteins, comprising any ubiquitin like domain and any reporter gene, and their methods of use for assessing the proliferative potential of malignant cells.

The structure and function of the claimed fusion proteins is not sufficiently described in the application. The Applicants teach a species of the claimed genus, which is the fusion protein comprising UbL^{R23}-lacZ, whose structure is known, however, the function as claimed i.e., to be used for assessing the proliferative potential of malignant cells, does not have support in Applicants' teachings:

"This fusion protein is undetectable in a strain expressing the oncogenic Ras mutant, while elevated levels of UbL^{R23}-lacZ were detected in cells lacking Ras", page 17 of the specification, line 13 and further.

Although one skilled in the art may agree with Applicants' conclusion: "These findings corroborate the proposal that UbL^{R23}-lacZ (SEQ ID NO: 3–lacZ) is a suitable reporter protein to assess the proliferative potential of cells." the language of the passage on page 17 suggests that in the reported experiment transformants of cells other than mammalian where used, because mammalian cells by nature possess the Ras gene wild type or mutated. Because Applicants do not provide definite results of degradation of UbL^{R23}-lacZ expressed in normal and malignant cells the claimed function of this protein is not supported.

The fusion proteins taught by Applicants such as Ub-P-ßgal or any other consisting of SEQ ID NOs: 2, 4-12 and operably linked reporter genes as claimed in claim 9, have not been transfected to malignant cells and their normal counterparts. Thus the function of these fusion proteins as claimed is not described in the specification.

As to the description of structure, the number of Ubl proteins is greater then disclosed in the application and therefore the scope of claims covers any Ubl. Thus, the genus of Ubl encoding DNA that is claimed to be used for construction DNA encoding fusion proteins is not sufficiently described. Provision of nucleic acid molecules that encode Ubl of SEQ ID NO: 2-11 is not sufficient for identifying all the species of the claimed DNA molecules encoding fusion proteins. In addition, the term "operably linked" as defined on page 19 does not state how the Ubl and reporter gene are connected. Thus, the term

"operably linked" is a generic terms covering many different connections that lack structural descriptions in the Application.

Given the lack of structural and functional characteristics of representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Furthermore claims 10-12 are rejected because step b) of claim 10 is lacking description of assessing the half-life of any fusion protein in a malignant cell, and its normal counterpart, transformed with DNA encoding said fusion protein. There is no data *in vitro* on any relationship between the half-life of any fusion protein and the rate of growth of malignant and normal cells transformed with DNA encoding fusion protein.

Because the lack of description of real experiments providing an evidence of relationship between the degradation of clamed fusion proteins in mammalian cells and their rate of growth, one skilled in the art is not convinced that Applicants were in possession of the claimed invention at the time the application was filed.

2.2.2. Lack of enablement

Claim 6-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a

way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to DNA constructs encoding fusion proteins comprising ubiquitin-like polypeptide and reporter protein peptide operably linked (Ubl-reporter) and their use for assessing the proliferative potential of malignant cells. The specification, however, fails to teach mammalian, normal and malignant, cells transformed with such DNA constructs and any data related to degradation of expressed fusion peptides in said mammalian cells. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses any DNA construct encoding for **Ubl-reporter**, or encoding for fusion wherein **Ubl** is any one of SEQ ID NO: 2-11 operably linked to any **reporter,** or any **Ubl** operably linked to **reporter that is** identified by claim 9, wherein said proteins are used in a method of assessing the proliferative potential of malignant cells.

The art of construction of DNA molecules encoding for fusion proteins is highly developed and skills of artisan high, however, because the structure of the

claimed fusion polypeptide to be used, and the method of use itself, are lacking enabling description (see the above rejection for lack of written description), one skilled in the art is forced to perform undue experimentation with low probability of success.

Since the degradation of any fusion protein in mammalian cells, normal and their malignant counterpart, is not disclosed, one skilled in the art would not know which fusion protein, i.e. its encoding DNA, to select for the method. The mechanism of degradation of linear molecules consisting of **Ubl-any protein** is not disclosed by Applicants. In yeast cells (Sacharomyces cerevisiae) the mechanism of degradation of fusion proteins is complex and involves so called N-end rule pathway and UFD pathway (Ub fusion degradation). Degradation of a particular **Ubl-reporter** depends on these two pathways and is affected by mutations in any of the genes in the pathways as well as primary and mutated structure of a **Ubl** used for fusion. In addition, the degradation depends on the link between the **Ubl** and the **reporter.** US patent 5, 132,213 discloses in Table 2, column 18 that the construct **ub**-Lys-**ßgal** has in S. cerevisiae the half-life of 3 min. **ub**-Met-Lys-**ßgal** more than 20 h; compare also Fig. 6 of the Patent. Thus, the half-life of any particular construct depends on its structure, and experimental conditions, i.e. particular normal and malignant cells to be used. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that the fusion proteins have the function to be used in the

method for assessing the proliferative potential of malignant cells. The disclosure fails to provide such guidance of the structure of DNA encoding fusion proteins and the guidance as to the malignant cells for which the use of said DNA is applicable; in result, experimentation left to those in the art is improperly extensive and undue.

2.3. 35 USC section 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 6, 7 and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by the US Patent 5,132,213, issued 1992.

The claims are directed to a DNA construct encoding a fusion protein comprising a first nucleic acid sequence encoding a Ubl domain operably linked to a third nucleic acid encoding a reporter gene, wherein said fusion protein is to be used for assessing the proliferative potential of malignant cells.

The patent discloses many constructs consisting of Ub (ubiquitin is a ubiquitin-like protein) and ßgal linked directly or through one or two amino acids.

The patent also discloses encoding DNA for such fusion protein and vector comprising said DNA; see Fig. 1, 6, and Table 2. The patent teaches the DNA as claimed in claims 6, 7 and 9. The patent does not teach the fusion protein for assessing the proliferative potential of malignant cells. However the limitation "for assessing the proliferative potential of malignant cells" in the preamble of claim 6 is not the internal feature of the fusion protein encoded by the claimed DNA construct and does not add the patentable weigh to the claim.

3. Conclusion

No claim is in conditions for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (571) 272-0944 and the right fax number is (571) 273-0944. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m. EST.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (571) 272-0928. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600